



## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Karouzakis et al. Atty Dkt: 1581/128  
Serial No: 09/762,602 Examiner: Hui,S.  
Date Filed: 3/21/01 Group No: 1617  
Invention: Use of Misoprostol or/and Date: October 15, 2002  
Misoprostol acid for preparing drug in order  
to cure sexual dysfunction in women.

#16  
PKD  
11/6/02

CERTIFICATE OF MAILING

I hereby certify that this correspondence addressed to the Commissioner for Patents, Washington, D.C. 20231 is being deposited with the United States Postal Service as first class mail on October 15, 2002.

  
Morton Chirnomas

Commissioner for Patents  
Washington, DC 20231

DECLARATION IN SUPPORT OF APPLICANTS' RESPONSE

[37 C.F.R. SECTION 1.132]

Dear Sir:

In support of the accompanying response to the May 15, 2002 office action in the above-referenced matter, I hereby declare as follows:

1. My name is Spiros Fotinos. I am Executive Vice President of Corporate Research and Innovation at Lavipharm SA and I am familiar with the work of Drs. Karouzakis and Kanakaris described and claimed in the present patent application for treating sexual dysfunction in women. My further qualifications are listed on the

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curriculum vitae which was previously submitted as Exhibit A with my Declaration dated October 23, 2001, and which is incorporated herein by reference.


2. I have reviewed the office action dated May 15, 2002, in the above matter and have considered the statement by the Examiner that it would have been obvious for one of ordinary skill in the art at the time the invention was made to apply a topical female sexual dysfunction treating composition of misoprostol with or without another vasodilator onto the vagina or clitoris. I respectfully disagree with the Examiner.

3. Drs. Karouzakis and Kanakaris have identified for the first time that misoprostol can be especially beneficial to women when applied topically. Drs. Karouzakis and Kanakaris have further identified for the first time properties of misoprostol which make it particularly useful for topical application. Misoprostol, in contrast with alprostadil and other PGE<sub>1</sub> analogues, has structural characteristics which impart (1) hydrophilicity, thereby facilitating its formulation in the absence of organic solvents that act as irritants, and (2) an ability to permeate through skin and mucosa to reach target tissue.

4. I have previously explained that the cited references invariably indicate a preference for PGE<sub>1</sub>/alprostadil. However, we now submit herewith data from studies in women, conducted by Drs. Karouzakis and Kanakaris and their colleagues, showing that the pharmacological activity of topically applied misoprostol was substantially superior to PGE<sub>1</sub> when topically applied. (see Appendix A). In summary, on a sample of 14 women, 71% showed a positive response to a 400µg dose of topically applied Misoprostol, versus a mere 7% response to a 25% ~~larger~~ 500 µg dose of PGE<sub>1</sub>. The level of response to the PGE<sub>1</sub> was equal to that for the placebo at 7% response.

6. I hereby declare that all statements made herein of my own knowledge and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of

the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

  
\_\_\_\_\_  
S. Fotinos

Dated: October 11, 2002

Exhibit A

Pharmacological effects of formulations on sexual dysfunction in female subjects having varying etiologies.

History (N)	I. Misoprostol*	II. PGE <sub>1</sub> **	III. Placebo***
Hormonal <sup>1</sup> (N=1)	1	0	0
Use of drugs <sup>2</sup> (N=4)	3	0	0
Diabetes <sup>3</sup> (N=2)	2	0	0
Vascular Disorders <sup>4</sup> (N=2)	1	0	0
Psychological problems (N=5)	3	1	1
total (N=14)	10 (71%)	1 (7%)	1 (7%)

<sup>1</sup> Hyperprolactinemia

<sup>2</sup> Cimetidine (N=2), Phenothiazines (N=2).

<sup>3</sup> Use of insulin & hypoglycaemic agents

<sup>4</sup> Hypertension/Use of  $\beta$ -blockers (N=1), Peripheral vascular diseases (N=1).

\* 0.5 ml Gel Misoprostol 400  $\mu$ g/0.5 ml.

\*\* PGE<sub>1</sub> 500  $\mu$ g in 0.5ml K-Y<sup>®</sup> Jelly for external use.

\*\*\* K-Y<sup>®</sup> Jelly (Johnson & Johnson).

Method: On 14 women, aged 25-55 years with sexual dysfunction of different causes, the following methods were applied successively for a few days up to 3 weeks.

- I. Topical application of 0.5 ml of Misoprostol Gel at 400  $\mu$ g/0.5 ml to the clitoris and vagina.
- II. Topical application of 0.5ml of PGE<sub>1</sub> at 500  $\mu$ g in 0.5ml K-Y<sup>®</sup> Jelly for external use to the clitoris and vagina.
- III. Topical application of 0.5 ml of K-Y Gel (J&J) as a placebo to the clitoris and vagina.



Practitioner's Desk No. 1581/128

**PATENT****IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Patent application

of \_\_\_\_\_  
Inventor(s)for \_\_\_\_\_  
Title of invention**OR**

In re application of: Kanakaris et al.

Application No.: 09/762,602

Group Art Unit: 1617

Filed: March 21, 2001

Examiner: Hui, S.

For: USE OF MISOPROSTOL OR/AND MISOPROSTOL ACID FOR PREPARING  
DRUG IN ORDER TO CURE SEXUAL DYSFUNCTION IN WOMEN**Commissioner for Patents  
Washington, D.C. 20231****TRANSMITTAL OF SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT  
BEFORE MAILING DATE OF EITHER A FINAL ACTION  
OR NOTICE OF ALLOWANCE (37 C.F.R. SECTION 1.97(c))****TIME OF TRANSMITTAL OF ACCOMPANYING  
SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**

1. The Supplemental Information Disclosure Statement transmitted herewith is being filed *after* three months of the filing date of this national application or the date of entry of the national stage as set forth in Section 1.491 in an international application or after the mailing date of the first Office action on the merits, whichever event occurred last but *before* the mailing date of either:

- (a) a final action under Section 1.113 or  
(b) a notice of allowance under Section 1.311,

whichever occurs first.

**STATEMENT OR FEE**

2. Accompanying this transmittal is

- A. ☒ a statement as specified in 37 C.F.R. Section 1.97(e).

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